REMARKS

Status of the claims

Claims 1-24, 37-53 and 64-82 are in the application.

Claims 37-53 have been withdrawn from consideration.

Claims 1-24 have been rejected.

An objection has been made to claims 64-82.

By way of this amendment, claims 1, 17, 64, 80, 81 and 82 have been amended, claims 37-53 have been canceled and new claims 83-113 have been added.

Upon entry of this amendment, claims 1-24 and 64-113 will be pending.

Summary of the Amendment

Claims 37-53 have been canceled as being directed toward a non-elected invention.

Claims 1 and 17 have been amended to correct an obvious error. Per the earlier amendment, claims 1 and 17 were not intended to be limited to methods performed on women suspected of being infertile only. The amendment of claims 1 and 17 correct an error in which reference to infertile women was erroneously kept in the claim language. Support for claims 1 and 17 is found throughout the specification, particularly at pages 14 and in the Examples. No new matter is added.

Claims 64, formerly dependent on claim 1, has been amended to be in independent form. As amended, claim 64 contains all of the limitations of claims 1 and 64.

Claims 80-82 have been amended to correct an obvious error. The correct name for the hormonal protocol referred to in claims 80-82 is a mock cycle, not a mock trial. Support for claims 80-82 is found throughout the specification, particularly at page 16, line 30 to page 17, line 11 and page 28, line 26 to page 34, line 6. No new matter is added.

New claims 83-97 correspond to claims 65-79 but are dependent on claim 80, which is directed at a method of claim 64 wherein the woman is undergoing a mock cycle, rather than being dependent directly on claim 64. Support for the invention is found throughout the specification. No new matter is added.

New claims 98-105 correspond to claims 17-24 with the express limitation that the method is performed on a woman suspected of being infertile. Support for new claims 98-105 is found throughout the specification and claims as originally filed, particularly claims 17-24 as originally filed. No new matter is added.

New claim 106 further limits claim 98 to those instances wherein the woman suspected of being infertile is undergoing a hormonal protocol to produce a mock cycle. Support for claim 106 is found throughout the specification, particularly at page 16, line 30 to page 17, line 11 and page 28, line 26 to page 34, line 6. No new matter has been added.

New claims 107-113 correspond to claims 99-105 but are dependent on claim 106, which is directed at a method of claim 98 wherein the woman is undergoing a mock cycle, rather than being dependent directly on claim 98. Support for the invention is found throughout the specification. No new matter is added.

Claims 37-53

Applicants acknowledge that claims 37-53 are deemed withdrawn as directed to non-elected inventions. Claims 37-53 have been canceled.

Claims 64-80

Claims 64-80 have been objected to as being dependent upon rejected claims. Claim 64 prior to the instant amendment is dependent on claim 1 and each of claims 65-80 are dependent on claim 64. As amended, claim 64 is an independent claim with all of the limitations of claims 1 and 64. As amended, the objection to claims 64-80 is moot and should be withdrawn.

Claim 1-24

Claims 1-24 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time the application was filed. It is asserted that "Applicant has no support for the

claims to "diagnosing any woman suspected of an abnormality in endometrial glandular development." It is pointed out that no specific guidance accompanied Applicant's earlier amendment pointing to where the support could be found.

Applicants respectfully point out that the specification supports the invention as broadly claimed in claims 1-24. Specifically, the specification at page 18 and in the Examples clearly indicates that the present invention arises from the discovery that the markers referred to in the claims can be used to evaluate endometrial glandular development. The most common reasons for evaluating endometrial glandular development are those described in detail in the specification, i.e. diagnosing and treating infertility and monitoring of hormone replacement therapy. However, the essence of the invention relates to the use of the methods to determine whether a woman is experiencing a normal endometrial glandular development or abnormal endometrial glandular development. The specification clearly reflects this central point of the invention on page 18, lines 20-23 (check page and line) stating:

> By detecting expression levels and cellular localization of markers at different time points in the menstrual cycle useful information can be gleaned and used in the diagnosis and treatment of patients being evaluated and treated for various conditions and disorder.

Accordingly, the broadening amendment of claims 1 and 17 filed in the earlier amendment are fully supported by the specification. The specification clearly indicates that the Applicant was, at the time the application was filed, in possession of the invention defined by claims 1-24. The specification clearly reflects that at the time the invention was filed, Applicants appreciated the invention as claimed. Applicants possessed the invention defined in claims 1-24, which refers to methods of diagnosing abnormality in endometrial glandular development by the steps recited therein. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-24.

Conclusion

Claims 1-24 and 64-113 are in condition for allowance. A notice of allowance is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Cancel 37-53 without prejudice, amend claims 1, 17, 64, 80, 81 and 82 and add claims 83-113 as follows.

1 (Twice Amended). A method of diagnosing an abnormality in endometrial glandular development in a woman comprising the step of:

detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from on or after day 20 of an idealized 28 day menstrual cycle from a woman; [suspected of being infertile;]
wherein

expression of cyclin E in the nuclei of greater than 5% of the gland cells indicates endometrial glandular developmental arrest, and/or

expression of cyclin E of greater than 1+ staining intensity in the cytoplasm of greater than 10% of the gland cells indicates endometrial glandular developmental arrest.

17 (Twice amended). A method of predicting abnormal endometrial glandular development comprising the steps of:

detecting the level of p27 in the nuclei of cells in a sample of endometrial tissue from day 10-18 of an idealized 28 day menstrual cycle from a woman [suspected of being infertile], and

comparing the level of expression with an expected level of expression;

wherein detection of elevated levels of p27 in the sample is predictive that the woman will be diagnosed with endometrial glandular developmental arrest.

64 (Amended). A method of <u>diagnosing an abnormality in endometrial glandular development in a</u> [claim 1 wherein said] woman [is] suspected of being infertile <u>comprising the step of:</u>

detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from on or after day 20 of an idealized 28 day menstrual cycle from said woman;[

wherein

expression of cyclin E in the nuclei of greater than 5% of the gland cells indicates endometrial glandular developmental arrest, and/or

expression of cyclin E of greater than 1+ staining intensity in the cytoplasm of greater than 10% of the gland cells indicates endometrial glandular developmental arrest.

80(Amended). A method of claim 64 wherein said woman is undergoing a hormonal protocol to produce a mock cycle. [trial.]

81(Amended). A method of claim 1 wherein said woman is undergoing a hormonal protocol to produce a mock cycle. [trial.].

82(Amended). A method of claim 17 wherein said woman is undergoing a hormonal protocol to produce a mock cycle. [trial.].

83 (New). The method of claim 80 wherein the expression of cyclin E is detected by an immunohistochemisty assay.

84 (New). The method of claim 80 wherein the cycle day is determined by examining the stroma cells in the sample.

85 (New). The method of claim 80 wherein expression of cyclin E is detected in the nuclei of greater than 10% of the gland cells in the sample is indicative of endometrial glandular developmental arrest.

86 (New). The method of claim 80 wherein the cycle day is day 24 of an idealized 28 day menstrual cycle.

87 (New). The method of claim 80 further comprising the step of detecting the expression of p27 in the nuclei of gland cells in a serial section of the sample.

88 (New). The method of claim 80 further comprising the step of detecting the expression of progesterone receptor in the gland cells in a serial section of the sample.

89 (New). The method of claim 80 further comprising the step of detecting the expression mouse ascites golgi mucin MAG in the gland cells in a serial section of the sample.

90 (New). The method of claim 80 further comprising the steps of detecting the expression of p27 in the nuclei of gland cells in a serial section of the sample and either detecting the expression of progesterone receptor in the gland cells in a serial section of the sample or detecting the expression of MAG in the gland cells in a serial section of the sample or both.

91 (New). The method of claim 80 further comprising the step of detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

92 (New). The method of claim 80 further comprising the step of detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from day 15 an idealized 28 day menstrual cycle from the woman.

93 (New). The method of claim 80 further comprising the step of detecting expression of p27 in the nuclei of endometrial gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

94 (New). The method of claim 80 further comprising the step of detecting expression of p27 in the nuclei of endometrial gland cells in an endometrial tissue sample from before day 17 of an idealized 28 day menstrual cycle from the woman wherein expression of p27 is indicative of accelerated endometrial glandular development.

95 (New). The method of claim 80 further comprising the step of detecting expression of progesterone receptor in the gland cells in an endometrial tissue sample from before day 18 of an idealized 28 day menstrual cycle from the woman.

96 (New). The method of claim 80 further comprising the step of detecting the expression of MAG in the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

97 (New). The method of claim 80 further comprising at least two of the following steps of:

a. detecting the expression of cyclin E in the nuclei and/or cytoplasm of the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

b. detecting the expression of p27 in the nuclei of gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

c. detecting expression of progesterone receptor in gland cells in an endometrial tissue sample on or before day 18 of an idealized 28 day menstrual cycle from the woman;

d. detecting the expression of MAG in the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

wherein said two or more steps are performed on serial sections of the sample.

98 (New). A method of predicting abnormal endometrial glandular development in a woman suspected of being infertile comprising the steps of:

detecting the level of p27 in the nuclei of cells in a sample of endometrial tissue from day 10-18 of an idealized 28 day menstrual cycle from said woman, and

comparing the level of expression with an expected level of expression;

wherein detection of elevated levels of p27 in the sample is predictive that the woman will be diagnosed with endometrial glandular developmental arrest.

99 (New). The method of claim 98 wherein the expression of p27 is detected by an immunohistochemisty assay.

100 (New). The method of claim 98 wherein the cycle day is determined by examining the stroma, and gland cells in the sample.

101 (New). The method of claim 98 wherein the cycle day is day 15 of a an idealized 28 day menstrual cycle.

102 (New). The method of claim 98 further comprising the step of detecting the expression of cyclin E in the nuclei and /or cytoplasm of gland cells in a serial section of the sample.

103 (New). The method of claim 98 further comprising the step of detecting the expression of progesterone receptor in the gland cells in a serial section of the sample.

104 (New). The method of claim 98 further comprising the step of detecting the expression MAG in the gland cells in a serial section of the sample.

105 (New). The method of claim 98 further comprising at least two of the following steps of:

a) detecting the expression of cyclin E in the nuclei and/or cytoplasm of the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

b) detecting expression of progesterone receptor in gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

c) detecting the expression of MAG in the gland cells in an endometrial tissue sample on or before day 18 of an idealized 28 day menstrual cycle from the woman;

wherein said two or more steps are performed on serial sections of the sample.

106 (New). A method of claim 98 wherein said woman is undergoing a hormonal protocol to produce a mock trial.

107 (New). The method of claim 106 wherein the expression of p27 is detected by an immunohistochemisty assay.

108 (New). The method of claim 106 wherein the cycle day is determined by examining the stroma, and gland cells in the sample.

109 (New). The method of claim 106 wherein the cycle day is day 15 of a an idealized 28 day menstrual cycle.

110 (New). The method of claim 106 further comprising the step of detecting the expression of cyclin E in the nuclei and /or cytoplasm of gland cells in a serial section of the sample.

111 (New). The method of claim 106 further comprising the step of detecting the expression of progesterone receptor in the gland cells in a serial section of the sample.

112 (New). The method of claim 106 further comprising the step of detecting the expression MAG in the gland cells in a serial section of the sample.

113 (New). The method of claim 106 further comprising at least two of the following steps of:

a) detecting the expression of cyclin E in the nuclei and/or cytoplasm of the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

b) detecting expression of progesterone receptor in gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

c) detecting the expression of MAG in the gland cells in an endometrial tissue sample on or before day 18 of an idealized 28 day menstrual cycle from the woman;

wherein said two or more steps are performed on serial sections of the sample.